SUPPORT FOR AMENDMENTS

The amendments to the specification were made solely to correct typographical errors.

The amendment to claim 7 is fully supported by the description in the specification (e.g., page 10, lines 4-7; etc.).

The amendments to claim 18 was made to correct a typographical punctuation error and for clarification.

The amendments to claim 19 were made solely for clarification, and are fully supported by the description in the specification (e.g., page 8, line 23 to page 9, line 24).

No new matter has been added. Upon entry of this Response, claims 7 and 18-20 remain present and active in the application, with claims 1-6 and 12-16 being presently withdrawn.

REMARKS

By way of introduction, the claimed invention is directed to methods of inducing the expression of a phase II enzyme in a subject. Independent claim 7 recites administering specific chloroform-soluble fractions of *Echinacea purpurea* to a subject —fractions that Applicants have shown provide a surprisingly and unexpectedly high induction of phase II enzymes, as described in the specification and as further explained below.

None of the applied references, alone or in combination, teaches or suggests the administration of the claimed fractions to a subject, as required by independent claim 7. Moreover, none of the applied references teaches or suggests the claimed chloroform root fraction and acidic chloroform aerial fraction, as further required by independent claim 7.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

1. The rejection of claims 18 and 19 under 35 U.S.C. § 112, second paragraph as being indefinite has been obviated by amendment.

Claim 18 has been rewritten to include an inadvertently omitted period at the end of the claim.

Claim 19 has been rewritten to clarify that the recitation of 0.09 mg/ml refers to a concentration of a chloroform-soluble *Echinacea* fraction in a medium in which the fraction is contained.

For the reasons set forth above, withdrawal of these grounds of rejection is respectfully requested.

2. The rejection of claim 20 under 35 U.S.C. § 112, second paragraph as being indefinite is respectfully traversed.

Claim 20 recites that the phase II enzyme induced by the method of claim 18 has a quinone reductase activity of about 1.86 at 610 nm. Base claim 18 does not recite quinone reductase, one of several types of phase II enzymes (e.g., specification, page 3, lines 24-28), nor does it recite such a level of activity. As such, claim 20 further limits the recitation of claim 18 and is not indefinite.

Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 102

The rejection of claims 7 and 18-20 under 35 U.S.C. § 102(e) as being anticipated by *Raskin et al.* (U.S. Patent Publication No. US 2002/0132021 A1) is respectfully traversed. At a minimum, *Raskin et al.* does not teach or suggest administering any fraction of *Echinacea purpurea* to a patient, as required by independent claim 7. In addition, *Raskin et al.* fails to teach or suggest administering the specific chloroform-soluble fractions of *Echinacea purpurea* recited in independent claim 7, or indeed any procedures that would enable one to obtain these claimed fractions.

Raskin et al. describes the combinatorial screening of an enormous number of plant species (e.g., paragraphs 13, 73, 74, 165, 166, 180, 181, etc.; Tables 2-7) in an effort to identify compounds produced by the plants that are potentially therapeutically useful. However, *Raskin et al.* is focused entirely on an evaluative screening process and is completely silent with respect to the administration of any of the tested plant compounds to a patient. Moreover, *Raskin et al.* certainly does not teach or suggest administering any fraction of any species of *Echinacea* to a patient, and is completely silent with respect to the induction of phase II enzymes in a patient.

Rather, *Raskin et al.* describes methods of eliciting chemical compounds in plants by treating the plants with an elicitor, such as acetic acid, which induces or improves production of the compounds from the plant (e.g., paragraphs 7, 14, 52-56, etc.). Once production of the desired compounds has been thus induced, the compounds may be then recovered from the plant by extraction, most typically into an aqueous medium (e.g., paragraphs 58-66, etc.).

The sole mention of *Echinacea purpurea* in the entirety of *Raskin et al.* is made in reference to plants that exhibited no detectable activities whether or not they were first induced with acetic acid (e.g., paragraph 165: page 28, left column; page 29, left column). There is no teaching or suggestion as to how *Echinacea purpurea*, or indeed any of the many other hundreds of plant species described therein, could be extracted with chloroform to provide chloroform-soluble fractions in the sense of the claimed invention. On the contrary, the sole mention of chloroform in the entirety of *Raskin et al.* is made in reference to the removal of non-cellular cuticular material from the surface of a leaf (e.g.,

paragraphs 3, 67)—a process that is clearly distinct from the type of extraction described in the present application in order to obtain the claimed chloroform-soluble fractions of *Echinacea purpurea*—a process that involved chopping and dehydrating plant material and subjecting the separated root and aerial fractions to a series of different solvent extractions (e.g., specification, page 5, line 22 to page 8, line 15).

It should be noted that *Raskin et al.* clearly distinguishes between surface removal of cuticular material from a plant leaf—a process implied as being preferable in view of the rapidity and ease by which compounds can be collected for subsequent combinatorial screening—and "total tissue extraction"—a process described as being "complex," "costly and laborious" (e.g., paragraphs 3 and 5). Thus, even if *Raskin et al.* contained some teaching or suggestion to use chloroform as a solvent to extract the root and aerial portions of *Echinacea purpurea*—which Applicants submit that it does not—there would still be no teaching or suggestion to use the chloroform in a "total" extraction procedure of a type capable of providing the claimed chloroform-soluble fractions of *Echinacea purpurea*.

In order to establish that *Raskin et al.* teaches an "acidic chloroform aerial fraction" in the sense of the claimed invention, as argued by the Examiner (Office Action, page 3), it would be necessary to show that *Raskin et al.* teaches the use of an acid to acidify an aqueous extract of *Echinacea purpurea* prior to further extraction with chloroform (cf. specification, page 7, line 25 to page 8, line 10). However, *Raskin et al.* contains no teaching or suggestion of this kind. Rather, as noted above, the description of acetic acid in *Raskin et al.* is strictly limited to its use as an elicitor to induce or increase production of compounds from a plant by contacting, for example, the plant roots with the acetic acid (e.g., paragraph 52). There is no teaching or suggestion whatsoever that acetic acid or indeed any acid be used as part of an extraction protocol.

In summary, *Raskin et al.* does not teach or suggest administering any form or fraction of *Echinacea purpurea* to a patient, as required by independent claim 7, nor does it teach or suggest administering the specific fractions of *Echinacea purpurea* recited in independent claim 7. For at least these reasons, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious

in view of *Raskin et al.* Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

The rejection of claims 7 and 18-20 under 35 U.S.C. § 103(a) as being unpatentable over *Intelisano* (U.S. Patent No. 6,440,448 B1) taken with *Facino et al.* (*Il Farmaco* **1993**, *48*, No. 10, pp. 1447-1461) or *Raskin et al.* is respectfully traversed on at least the two grounds set forth below.

1. Failure to Establish a *Prima Facie* Case of Obviousness

The applied references, alone or in combination, fail to teach or suggest all of the limitations of independent claim 7. More specifically, these references fail to teach or suggest administering to a subject a chloroform root fraction and/or an acidic chloroform aerial fraction of *Echinacea purpurea* to induce the expression of phase II enzymes.

Intelisano describes a food supplement containing numerous plant- and/or animal-based ingredients, one of which may be *Echinacea purpurea* (e.g., col. 2, lines 18-46). However, there is no teaching or suggestion of extracting the specific chloroform-soluble fractions of *Echinacea purpurea* recited in independent claim 7, or of administering such fractions to a patient.

Facino et al. describes the use of mass spectrometry to identify compounds in *Echinacea angustifolia* that are responsible for its antihyaluronidase activity (e.g., page 1447, summary). Although an extraction procedure involving chloroform (among other solvents) is described for extracting active agents from *Echinacea angustifolia*, the fractions that were identified as having the highest antihyaluronidase activity were those extracted with butyl acetate and ethyl acetate—not the chloroform fractions (e.g., page 1458, second full paragraph). There is no teaching or suggestion of extracting the specific chloroform-soluble fractions of *Echinacea purpurea* recited in independent claim 7, or of administering such fractions to a patient.

Raskin et al., as noted above, describes the combinatorial screening of compounds obtained from plants following an induction process, and likewise contains no teaching or suggestion of either the specific claimed fractions of *Echinacea purpurea* or of the administration of such fractions to a patient.

Moreover, Applicants respectfully submit that the combination of *Intelisano*, *Facino et al.*, and *Raskin et al.* does not establish a *prima facie* case of obviousness inasmuch as the suggestion and motivation to modify or combine their respective teachings is lacking and must be derived from Applicants's disclosure, which alone provides the suggestion and motivation for achieving induction of phase II enzymes in a patient. In accordance with MPEP 2143, Applicants note that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Each of *Intelisano*, *Facino et al.*, and *Raskin et al.* is completely silent with respect to the induction of phase II enzymes in a subject. However, in order to discover that the claimed chloroform-soluble fractions of *Echinacea purpurea* exhibit the highest activity of phase II enzyme induction and, therefore, are desirable for use in the claimed methods of inducing expression of phase II enzymes, one would first have to be seeking to achieve higher levels of phase II induction. None of *Intelisano*, *Facino et al.* or *Raskin et al.* provides or suggests such a motivation.

On the contrary, based on the teachings of *Raskin et al.*, one would conclude that *Echinacea purpurea* is a poor candidate for providing therapeutically active compounds since compounds obtained therefrom exhibited no detectable activity whether or not they were first induced with acetic acid (e.g., paragraph 165; page 28, left column; page 29, left column). Similarly, based on the teachings of *Facino et al.*, one would conclude that the most active compounds from *Echinacea purpurea* would be those extracted using butyl or ethyl acetate—not chloroform (e.g., page 1458, second full paragraph). In both instances, these erroneous conclusions would prevent one from discovering that root portions of *Echinacea purpurea* extracted with chloroform and aerial portions of *Echinacea purpurea* extracted with acidic chloroform provide the claimed chloroform-soluble fractions having surprisingly and unexpectedly high induction of phase II enzymes.

For the reasons set forth above, Applicants respectfully submit that a *prima facie* case of obviousness based on the combination of *Intelisano*, *Facino et al.*, and *Raskin et*

al. has not been established. Accordingly, withdrawal of this ground of rejection is respectfully requested.

2. Secondary Considerations of Non-Obviousness

Assuming *arguendo* that a *prima facie* case of obviousness based on the combination of *Intelisano*, *Facino et al.*, and *Raskin et al.* had been established, which Applicants respectfully submit that it has not—this hypothetical *prima facie* case would be rebutted by the surprising and unexpected results provided by the claimed invention, which are described in the specification. As required by MPEP 2141, "[o]bjective evidence or secondary considerations such as unexpected results ... are relevant to the issue of obviousness and must be considered in every case in which they are present."

Applicants have shown that certain fractions of *Echinacea*, particularly the lipid-soluble fractions, show a greater induction of phase II enzymes than other fractions (e.g., specification, page 1, lines 13-15). For the roots, the fraction with the greatest induction activity is the chloroform fraction, whereas for the aerial parts, the fraction with the greatest induction activity is the acidic chloroform fraction (e.g., specification, page 5, lines 11-14). The data in FIG. 2 demonstrates the surprisingly and unexpectedly high induction of phase II enzymes that was observed for these respective fractions:

> At this concentration of extract, the root fraction with the greatest quinone reductase induction activity was the chloroform (1) fraction with activity at 1.86 times the level of the control. The aerial parts fraction with the greatest quinone reductase induction activity was the acidic chloroform (2) fraction with activity 1.74 times that of control. For the roots, the level of enzyme activity in the root chloroform (1) fraction was 35% higher than the root 80% methanol fraction. Likewise, for the aerial parts, the level of enzyme activity in the acidic chloroform (2) fraction was 86% higher than the more polar fraction extracted with 80% methanol. (specification, page 9, line 25 to page 10, line 3)

The Examiner has dismissed Applicants's assertion of surprising and unexpected results as being "inconclusive" on the basis that in FIG. 2, "the root fraction activity using acidic chloroform is lower than using petroleum ether" (Office Action, pages 4-5). Applicants respectfully submit that this comparison is misdirected since, as noted above, the root fraction with the greatest induction activity was found to be the chloroform fraction—not the acidic chloroform fraction as implied by the Examiner. FIG. 2 clearly

shows that the highest level of induction activity observed for any root fraction corresponds to the chloroform (1) fraction; moreover, the level of enzyme activity in the root chloroform (1) fraction was 30% higher than in the root petroleum ether fraction. Accordingly, Applicants respectfully submit that the data are not inconclusive and that the description and examples in the specification (e.g., page 8, line 17 to page 10, line 7; FIG. 2; etc.) serve as objective evidence of nonobviousness in accordance with MPEP 716.01(a) and 2144.08.

Inasmuch as the above-described data serve as objective evidence of nonobviousness in accordance with MPEP 716.01(a) and 2144.08, Applicants respectfully submit that a hypothetical case of prima facie case of obviousness would be overcome. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 7 and 18-20 under 35 U.S.C. § 103(a) as being unpatentable over *Raskin et al.* is respectfully traversed for at least the reasons set forth above in the remarks directed to the rejection under 35 U.S.C. § 102(e) based on this same reference.

At a minimum, *Raskin et al.* does not teach or suggest administering any fraction of *Echinacea purpurea* to a patient, as required by independent claim 7. In addition, *Raskin et al.* fails to teach or suggest administering the specific chloroform-soluble fractions of *Echinacea purpurea* recited in independent claim 7, or indeed any procedures that would enable one to obtain these claimed fractions.

For at least these reasons, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Raskin et al.* Accordingly, withdrawal of this ground of rejection is respectfully requested.

Conclusion

In view of the Amendment and Remarks set forth above, Applicants respectfully submit that the claimed invention is in condition for allowance. Early notification to such effect is earnestly solicited.

If for any reason the Examiner feels that the above Amendment and Remarks do not put the claims in condition to be allowed, and that a discussion would be helpful, it is

respectfully requested that the Examiner contact the undersigned agent directly at (312)-321-4257.

Respectfully submitted,

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